VIII SIMPOSIUM
ICAPEM
Madrid, **7** de **noviembre** de 2024
PRESENCIAL
RETRANSMITIDO EN DIRECTO

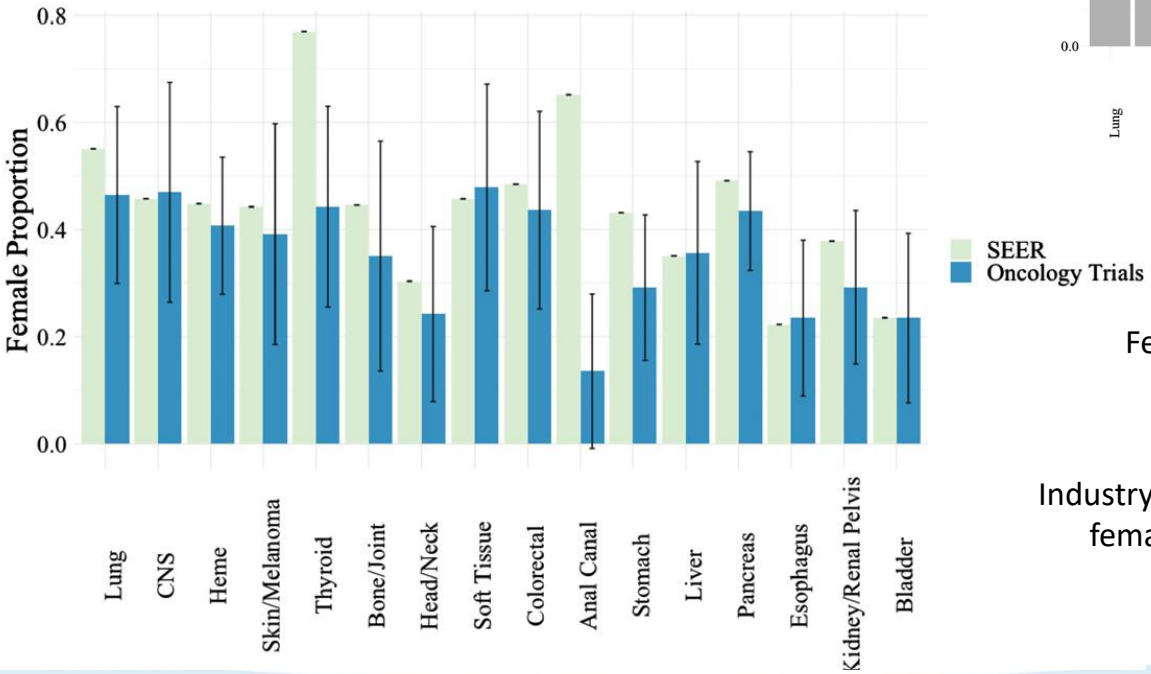
GENDER EQUITY IN CLINICAL TRIAL: SURVEY ON PERCEPTION OF PATIENT ENGAGEMENT STATUS IN CLINICAL TRIALS (ENGAGE Study)

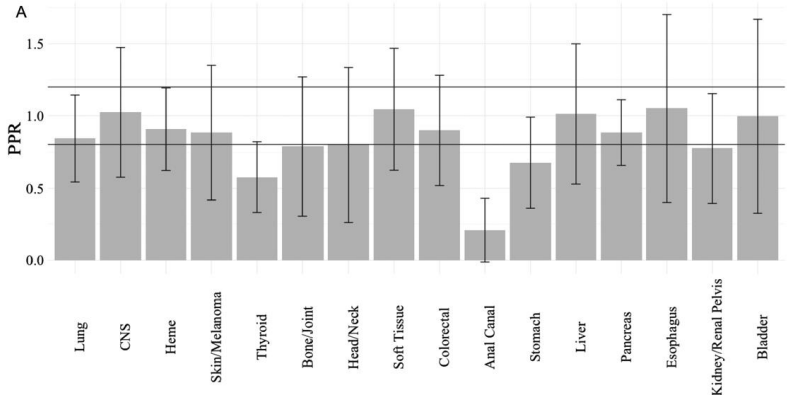
Dr. Maristella Bungaro, *Italy*

Analysis of Female Participant Representation in Registered Oncology Clinical Trials in the United States from 2008 to 2020

1650 trials consisting of 240,776 participants

Primary EP: participation to prevalence ratio (PPR)





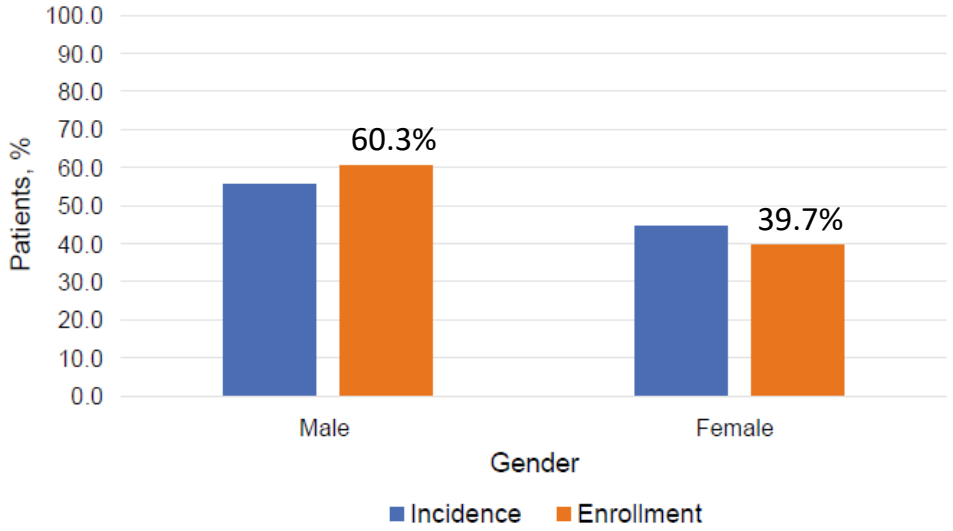
Females represented 46.9% of participants (95% CI, 45.4-48.4)

Industry-funded trials had greater odds of proportional female representation than US government and academic-funded trials.

Perera ND, The oncologist 2023

Assessment of Gender Representation in Clinical Trials Leading to FDA Approval for Oncology Therapeutics Between 2014 and 2019: A Systematic Review-Based Cohort Study

149 clinical trials
59,988 participants
127 drug approvals



Comparison of male and female oncology clinical trial enrollment with US cancer incidence from 2014 to 2019.

Overall, women were underrepresented when compared with expected incidence (EID, +4.9%; 42% of trials), particularly for thyroid cancer

Dymanus KA, Cancer 2021

Male or Female... IS THAT ENOUGH TODAY?

Awareness of the impact of sex and gender in the disease risk and outcomes in hematology and medical oncology—a survey of Swiss clinicians

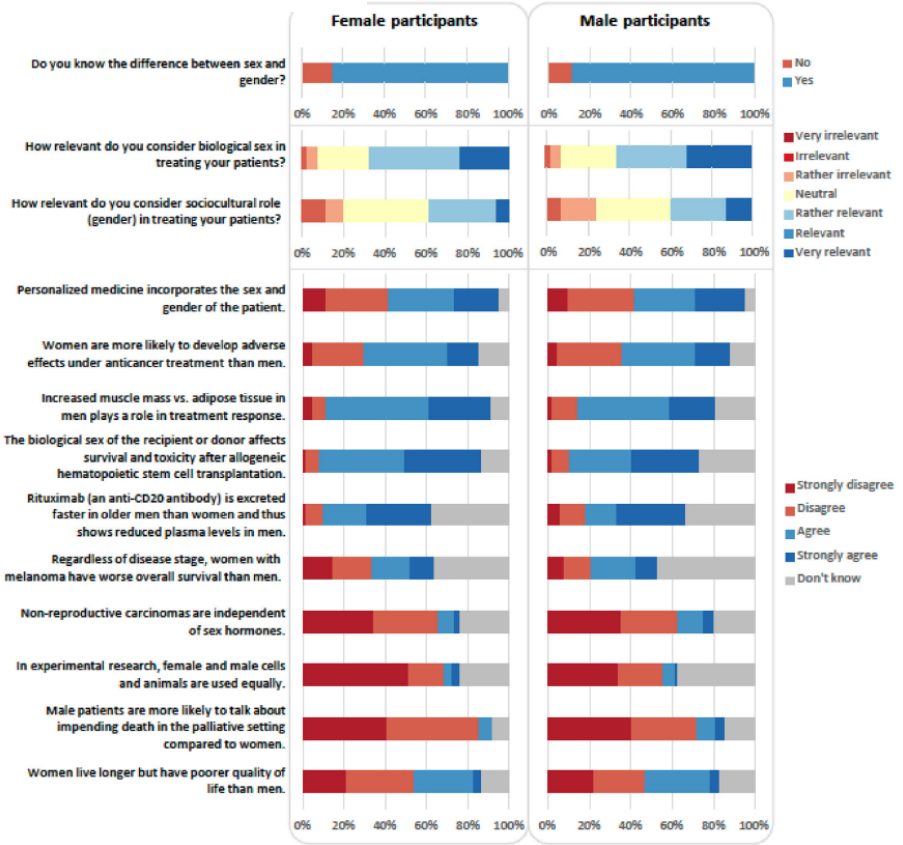
767 eligible clinicians - 20% response rate

Most participants agreed that sex and gender were relevant when treating patients

BUT…

Few participants knew about sex and gender differences in treatment toxicity and survival

Most participants agreed that this topic should be integrated into continuing education and research.



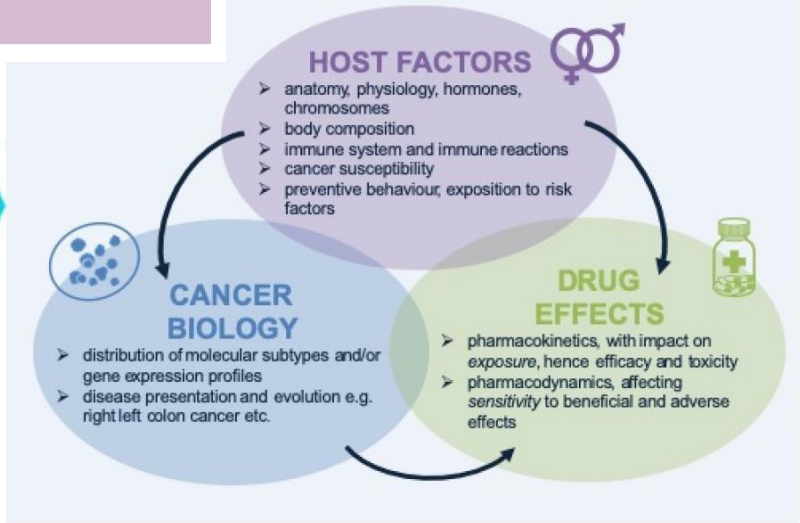
Darphin X, Cancer Reports 2024

Gender medicine and oncology: report and consensus of an ESMO workshop

Lausanne, Switzerland, 2018

Clinically relevant sex differences include tumor biology, immune system activity, body composition and drug disposition and effects.

AGE



Sex differences in cancer biology and treatment deserve more attention and systematic investigation

Interventional clinical trials evaluating sex-specific dosing regimens are needed to improve the balance between drug efficacy and toxicity.

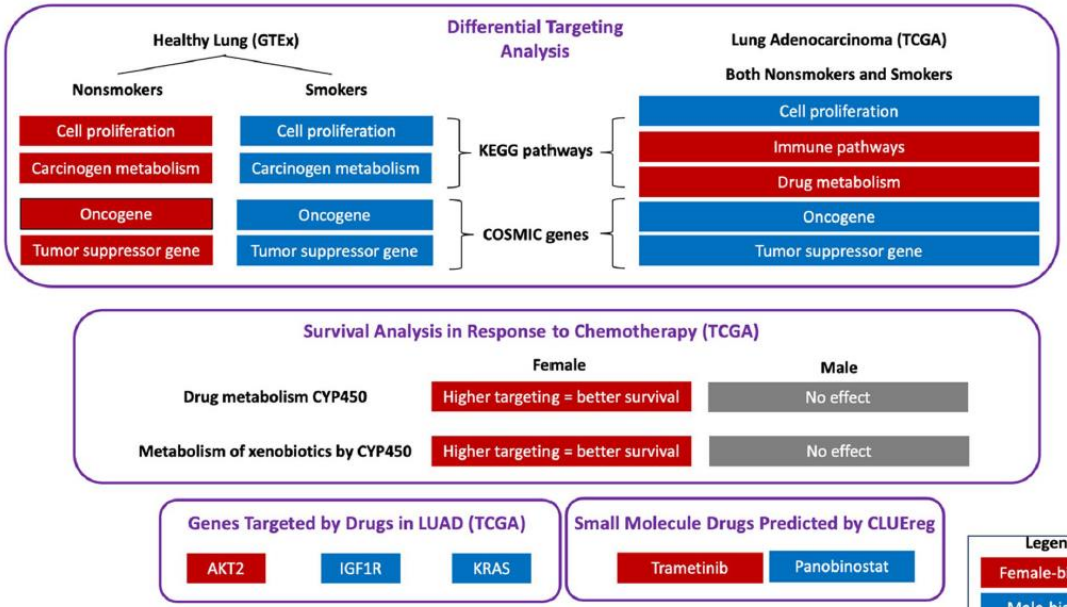
Men and women with sex-unrelated cancers should be considered as biologically distinct patient groups for whom specific therapeutic approaches deserve to be considered.

The Gender Medicine Task Force was launched in 2019

Wagner AD, Annals of Oncology 2019

Gene regulatory networks reveal sex difference in lung adenocarcinoma

Genes associated with cell proliferation, immune response, and drug metabolism are differentially regulated between males and females both in healthy lung tissue and lung cancer samples.
Regulatory differences are further perturbed by tobacco smoking.



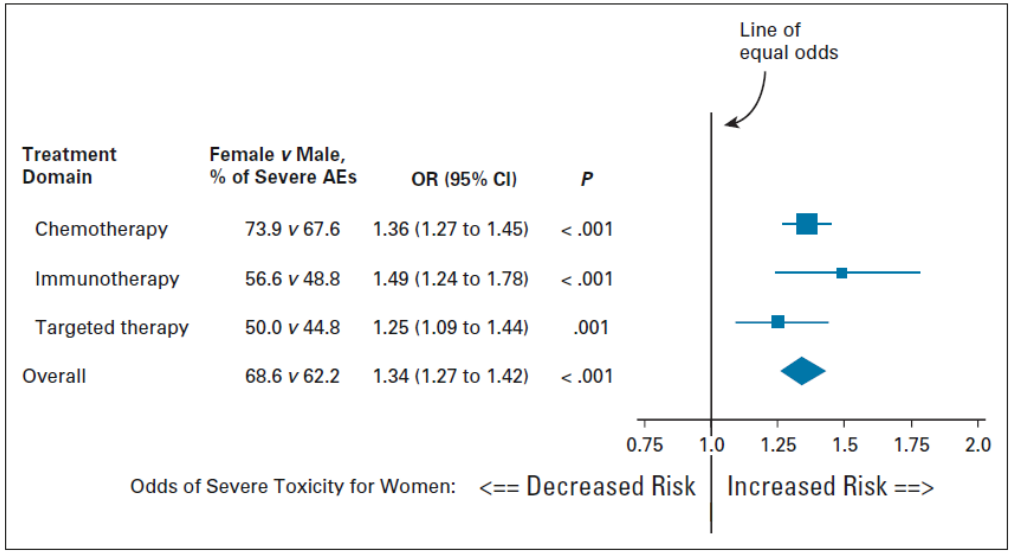
Sex bias exists in transcription factor targeting patterns of actionable oncogenes and tumor suppressor genes including *AKT2* and *KRAS*.

Several small-molecule drugs that might have sex-biased efficacy were identified.

Saha E, Biology of Sex Differences 2024

Sex Differences in Risk of Severe Adverse Events in Patients Receiving Immunotherapy, Targeted Therapy, or Chemotherapy in Cancer Clinical Trials

N 23296 pts
F 37.9%, M 62.1%
202 ph II-III trials
1980-2019



Overall, 64.6% pts experienced ≥ 1 severe AEs.

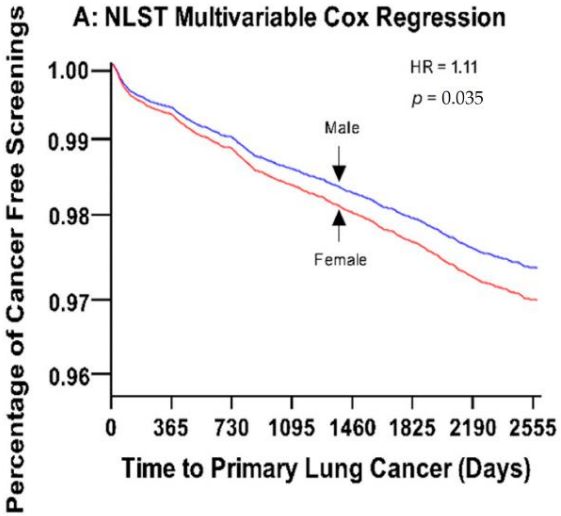
Women had a **34% increased risk of severe AEs** compared with men (odds ratio 1.34; 95% CI, 1.27 to 1.42; P .001), particularly **haematological** AEs.

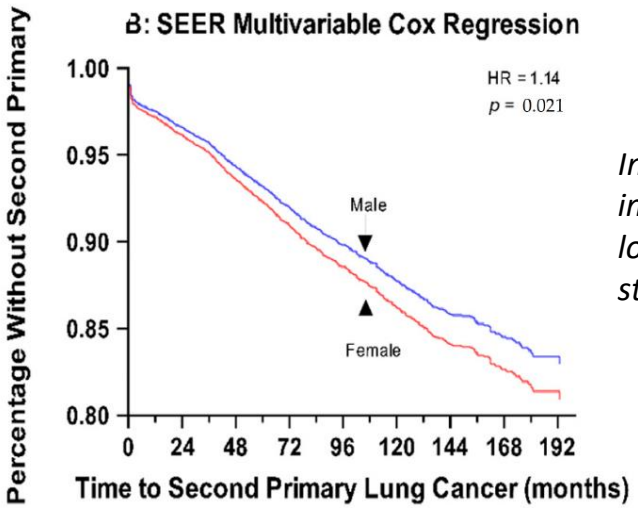
Women experienced an increased risk of **symptomatic** AEs among all treatments, especially **immunotherapy**.

Unger JM, J Clin Oncol 2022

Sex-Based Differences in Lung Cancer Incidence: A Retrospective Analysis of Two Large US-Based Cancer Databases

Incidence of LC among individuals with a smoking history of ≥ 40 p/y in the NLST





Incidence of 2° NSCLC in pts who underwent lobectomy for previous stage I LC in SEER DB.

NLST cohort (n = 37,627)

F had a higher risk of developing primary NSCLC (HR = 1.11 [1.007–1.222], p = 0.035) after adjusting for age and p/y history.

SEER cohort (n = 19,327)

F exhibited an increased risk of developing a 2° primary LC (HR = 1.138 [1.02–1.269], p = 0.021), after adjusting for age, race, grade, and histology.

Ratnakaram K, Cancers 2024

ESMO Open Cancer Horizons

Gender and sex disparity in cancer trials

What can be the possible obstacles to enrolling women in clinical trials?

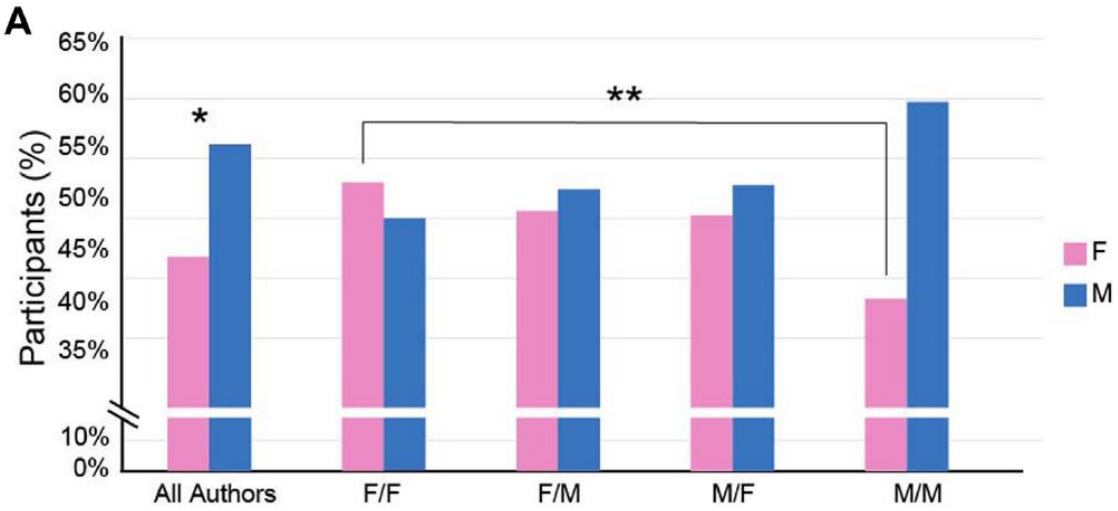
- **limited awareness** of trial opportunities
- limited **trial availability** at the treating institution
- overly stringent **eligibility criteria**
- **study burden and inconvenience** (increased office visits, greater travel requirements, need to maintain daily logs or specific treatment regimens, disruptions on daily lives, family responsibilities)
- **distrust of researchers** and research institutions
- **lack of understanding** about the role of clinical research
- fear of **risk and randomization**
- negative attitudes towards women as study participants from **sponsors and medical professionals**
- **ineffective doctor-patient relationship**

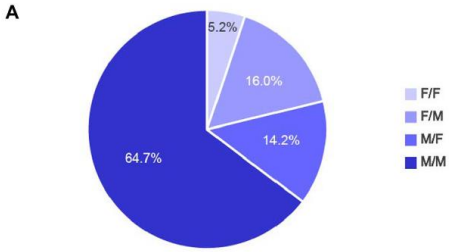
Lee E, ESMO Open 2020

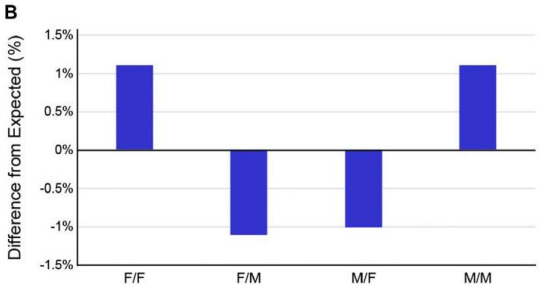
Gender Bias in Clinical Trial Enrollment: Female Authorship Matters

1,427 articles published in the JAMA, The Lancet, and the NEJM from 2015 to 2019

F 2,104,509 (44.6%) / M 2,616,981 (55.4%)







Proportion of females enrolled decreased with the following first and senior author pairings:

F/M (48.9%)

M/F (48.6%)

M/M (40.5%, P 0.0001 compared to F/F authorship)

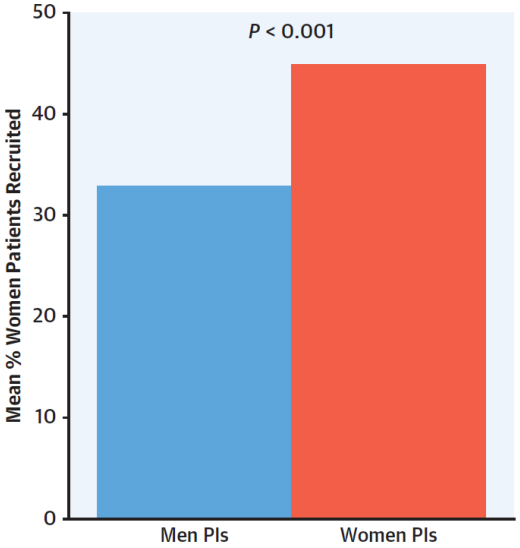
More F were enrolled if both first and senior authors were female (51.7%).

Surgical oncology had the highest female enrollment with female-female authorship.

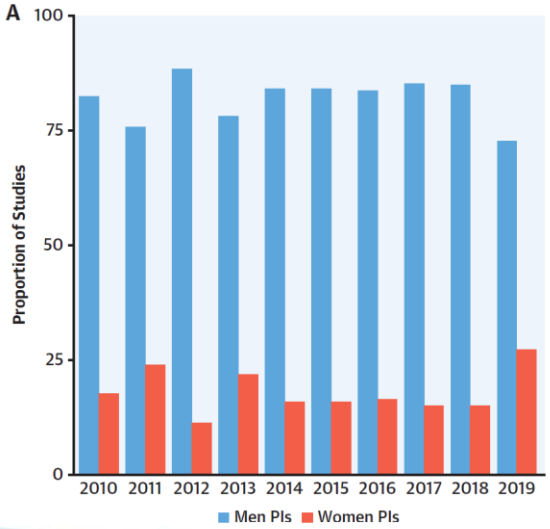
Chhaya VY, Ann Vasc Surg 2023

Letter

Temporal Trends in Gender of Principal Investigators and Patients in Cardiovascular Clinical Trials



Compared with studies led by men, those led by women enrolled more female participants (44.9% vs 37.9%; P < 0.001)



Has equity in clinical trial leadership improved over time?

The proportion of clinical cardiovascular trials led by women has not increased over the past decade!

Yong C, JACC journals 2023

Many pharmaceutical companies are recently showing interest in the topic!

Diversity and Representation Among United States Participants in Amgen Clinical Trials

E. Racquel Racadio[1] · Angshu Rai[1] · Pinar Kizilirmak[1] · Sonali Agarwal[1] · Eloy Sosa[1] · Claire Desborough[2] · Tatheer Adnan[1] · Lei Zhou[1] · Akhila Balasubramanian[1] · Anushree Sharma[1] · Ponda Motsepe-Ditshego[1]

M representation disproportionately higher than F between 2016-2020

Demographic diversity of participants in Pfizer sponsored clinical trials in the United States

F participation ≃ at US census (51.1% vs 50.8%)

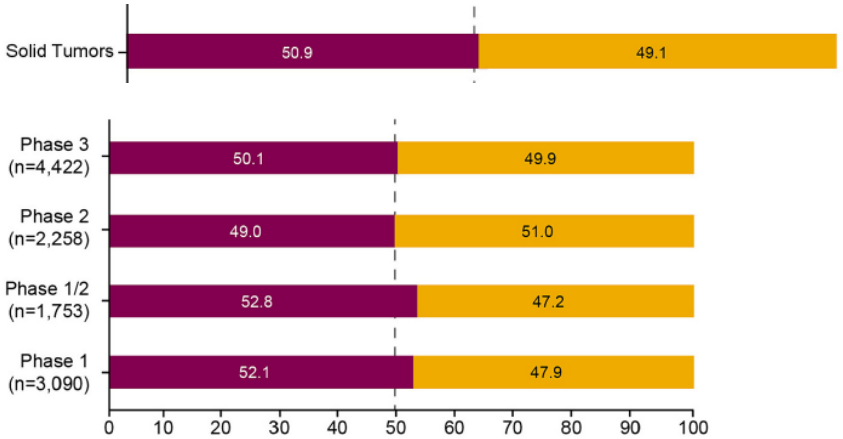
Demographic diversity of US-based participants in GSK-sponsored interventional clinical trials

Focus on racial and ethnic demographic diversity

Diversity of US participants in AstraZeneca-sponsored clinical trials

Claudia Cabrera[a,*], Daniel Fernández-Llaneza[b], Zara Ghazoui[c], Sofia D'Abrantes[c], M. Alejandro Esparza-Franco[c], Charles Sopp[b], Beata Maj[d], Victoria L. Chiou[e], Barbara Valastro[f], Menelas N. Pangalos[g], Susan Galbraith[e], Serban Ghiorghiu[h], Cristian Massacesi[i]

Parity in the proportions of M and F between trials and US Census (M 52.4% vs 49.2%, F 47.6% vs 50.8%)



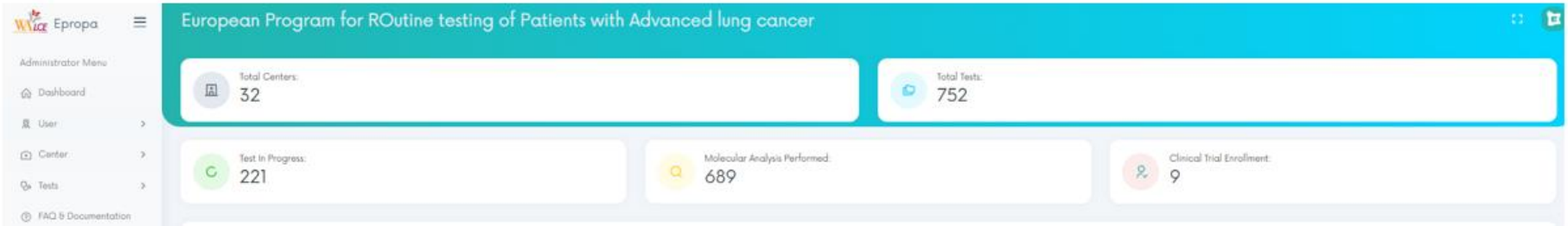
Publication date 2021-2024

EPROPA- European Program for ROutine testing of Patients with Advanced lung cancer)

Increasing Patient Access to NGS-molecular screening

Increasing Patient Access to biomarker-driven clinical trials

Updating 31.10.2024



ENGAGE Trial: Evaluating Needs and Gaining Equality in Clinical Trials for Gender Equity

Study promoting center:

- Department of Medical Oncology, University of Turin, San Luigi Gonzaga Hospital, Orbassano (TO), Italy.

Principal Investigator and coordinator study center:

- Prof. Silvia Novello, University of Turin - San Luigi Gonzaga Hospital.

ENGAGE Trial

There are currently **no prospective studies in the literature** that have assessed a possible gender imbalance in enrolment in clinical trials.

Ensuring a representative data collection of the real population is important for achieving generalizability and reproducibility of trial data and **reducing disparities in healthcare**.

Gender should be recognized as an **important variable in research**, and knowledge in this field should be enhanced.

Study design - Multicenter, cross-sectional/prospective, observational study

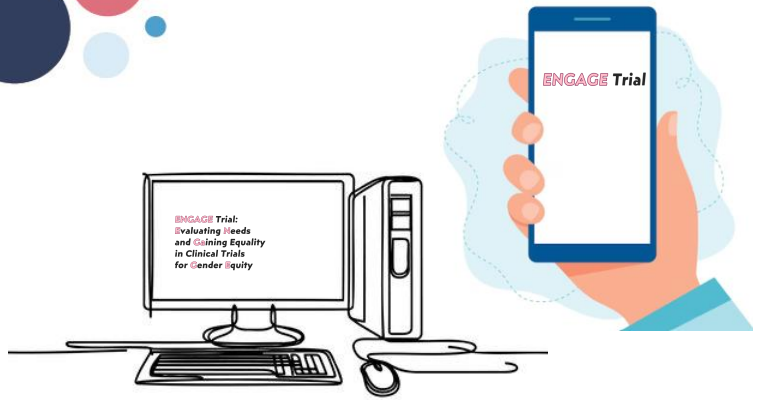
17 Italian centres

14 International centres

Spain (6)
France (3)
Israel (3)
Netherlands (1)
Greece (1)

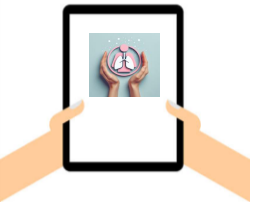
<u>Centers with active clinical trials for patients affected by lung cancer</u>

at any stage could be recruited



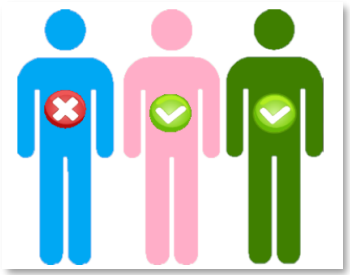
Survey respondents

Oncologists will be interviewed through a survey via an electronic web application, assessing daily the possibility of enrolment in clinical trials for lung cancer patients.



Inclusion criteria for patient evaluation in the e-survey:

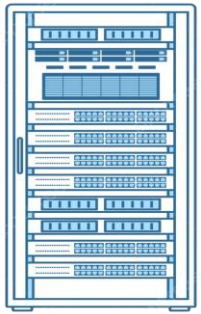
- Males/females ≥18 y with histologically confirmed diagnosis of primary lung cancer (any histology and stage)
- Patient evaluated in decision-making visits (for any intervention approach and treatment line).



Eligible clinical trial

All the trials that require a lung cancer diagnosis in the inclusion criteria can be considered and proposed by the oncologists.

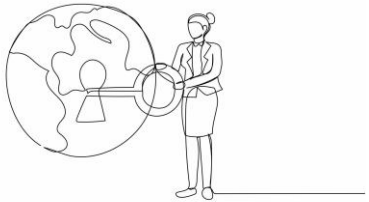
Ethical considerations and privacy



“GenderEquity” e-CRF is generated via the use of the meta-platform L.I.S.A.

The server of University of Turin will host the web application and data will not be shared via google, apple servers or any search engine.

Data ownership and protection will be guaranteed by the University of Turin.



The data of all participants, doctors and patients, will be **completely anonymized** with a progressive identification code generated automatically by the system.

Physicians and patients will provide informed consent for collecting personal records, data extraction-processing and statistical analysis.

Aim of the study

To describe the current inclination of medical oncologists in recruiting patients into clinical trials, with a focus on gender.

Primary endpoint

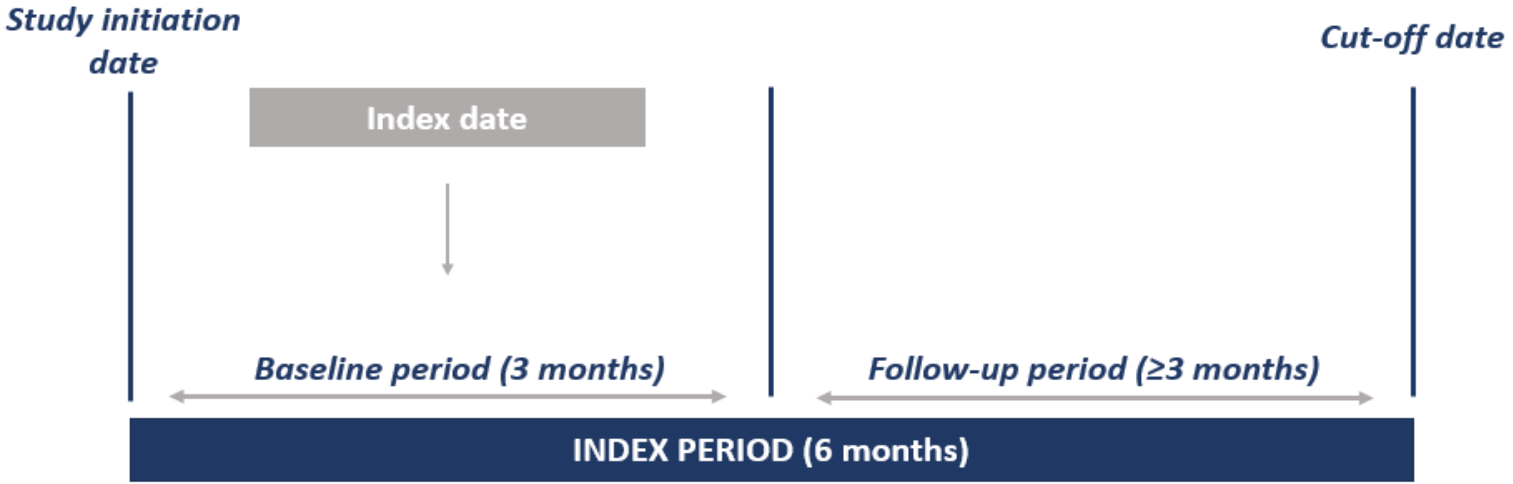
To describe and compare, among participating countries, the number of lung cancer patients offered a clinical trial and assess the enrolment rate according to gender.

Secondary endpoints aim to:

- ✓ assess the rate accrual within prespecified sub-groups, defined by psycho-social background, demographic, clinical and lung cancer characteristics;
- ✓ identify the main reasons for not proposing enrolment in clinical trials;
- ✓ describe the rate of patient withdrawal at specific time points and its correlation to the prespecified sub-groups;
- ✓ assess the rate of patient accrual according to the characteristics of oncologists (demographic and professional factors);
- ✓ assess the rate of patient accrual according to the characteristics of clinical trials (presence of randomization, phase, active comparator vs placebo, setting, sponsorship, other).

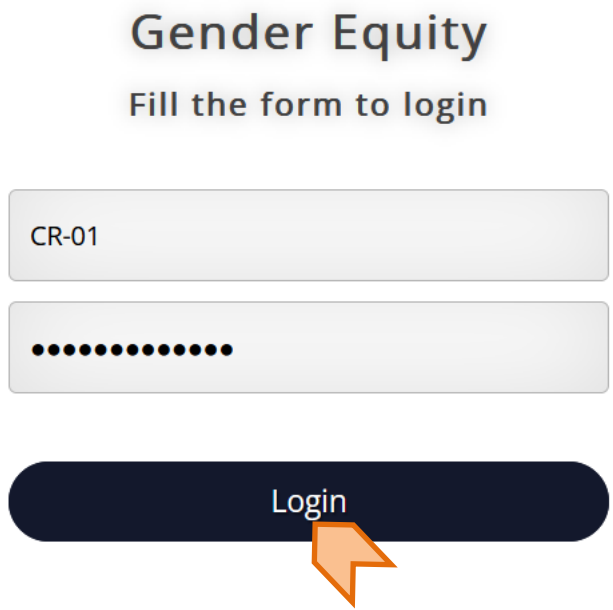
Structure and timing of the survey

- Patient demographic, social and clinical data
- Disease characteristics
- Details of the proposed clinical trial
- Any reasons for not considering trials or for patient refusal



For patients enrolled in clinical trials, study adherence will be collected at specific time points (1, 3, 6 months).

The WebApp



The WebApp – Home Page

Welcome CR-01

Logout

Clinical Trials | Oncologist

Insert below the patient screening code to apply the filter

No data to display

Add new patient

ENGAGE Trial

Clinical Trials

Clinical Trial: ADAURA — Delete — Edit

Clinical Trial: LAGOON — Delete — Edit

Add new Clinical Trial

Add new Clinical Trial

Clinical trial name or identification code

Study type

Phase

Stage

Intervention type

- [ ] Secondary or tertiary prevention (interventions with the aim of detecting a second cancer early or reducing the impact of ongoing disease)
- [ ] Procedural (procedures aimed at staging or defining the pathological and molecular characteristics of lung cancer - palliative procedures, etc.)
- [ ] Surgery
- [ ] Radiation
- [ ] Drug/treatment
- [ ] Behavioral

Blinding

Allocation status

Cross-over

Comparator arm

Lead sponsor

Save

Edit Oncologist

Age

<35

Gender

Female

Race

White

Ethnicity

Not Hispanic or Latino origin

Country

Italy

Marital status

Married

Experience (years)

<10

Type of institute

General hospitals

Avarage number of patients per day

10-19

Save

ENGAGE Trial

Add new patient

- Patient Information
- Clinical Characteristics
- Lung Cancer Characteristics
- Details of Clinical Trial

Patient Information

Screening Code: 0001

Birthdate: dd/mm/yyyy

Gender

Race

Patient Creation Date: dd/mm/yyyy

Ethnicity

Country

Education

Marital status

Children

Working status

Alcohol intake

Smoking status

Drug abuse

Dedicated caregiver

Awareness of diagnosis and prognosis

Previous enrollment in clinical trial

Supported by patient advocacy group

ENGAGE Trial

Clinical Characteristics

PS ECOG

Comorbidities

- [ ] None
- [ ] Cardiovascular
- [ ] Respiratory
- [ ] Neurological
- [ ] Autoimmunity
- [ ] Metabolic
- [ ] Gastrointestinal disorders

Psychiatric disorder

Severe symptoms

- [ ] No
- [ ] ≥G3 CTCAE dyspnoea (G3 shortness of breath at rest, limiting self care ADL, urgent intervention indicated)
- [ ] G3 CTCAE pain (G3 severe pain - limiting self care ADL)
- [ ] ≥G3 CTCAE asthenia (≥G3 fatigue not relieved by rest, limiting self care ADL)

Lung Cancer Characteristics

Histology

Stage

Proposed intervention type (after the decision-making visit)

- [ ] Procedural (procedures aimed at staging or defining the pathological and molecular characteristics of lung cancer - palliative procedures, etc.)
- [ ] Therapeutic approach (surgery, radiotherapy, systemic treatment...)
- [ ] Behavioral
- [ ] Dietary supplement
- [ ] Supportive care
- [ ] Palliative care for endstage disease

Presence of oncogene addiction

ENGAGE Trial

Details of Clinical Trial

Clinical trial proposed to the patient

Yes

Patient sent by another center for clinical trial

Select clinical trial(s) proposed to the patient

- [ ] ADAURA
- [ ] LAGOON

Details of Clinical Trial

Clinical trial proposed to the patient

No

Reason(s) for not considering clinical trials

- No trial available in my centre
- No trial available in my regional/national territory
- Not eligible for unsatisfied inclusion/exclusion criteria
- No time for discuss clinical trial
- Patient reluctance to discuss the subject
- Other

ENGAGE Trial

- Patient Information
- Clinical Characteristics
- Lung Cancer Characteristics
- Details of Clinical Trial
- Follow-up
  - Follow-up - 1 months
  - Follow-up - 3 months
  - Follow-up - 6 months

Follow-up - 1 months

Follow-up creation date

dd/mm/yyyy

Does the patient still participate to the clinical study?

Yes

No

Save

ENGAGE Trial

Does the patient still participate to the clinical study?

No

Why does the patient no longer participate in the clinical trial?

- Clinical reasons
- Investigator decision
- Patient decision to withdraw
- Other

Select (clinical reasons)

Select (investigator decision)

Select (patient decision to withdraw)

- Personal issues
- Concerning about adverse events
- Negative economic impact
- Medical mistrust or aversion to procedures
- Excessive time consuming (frequent visit schedule and examination)
- Lack of understanding
- Distance between home and research institute

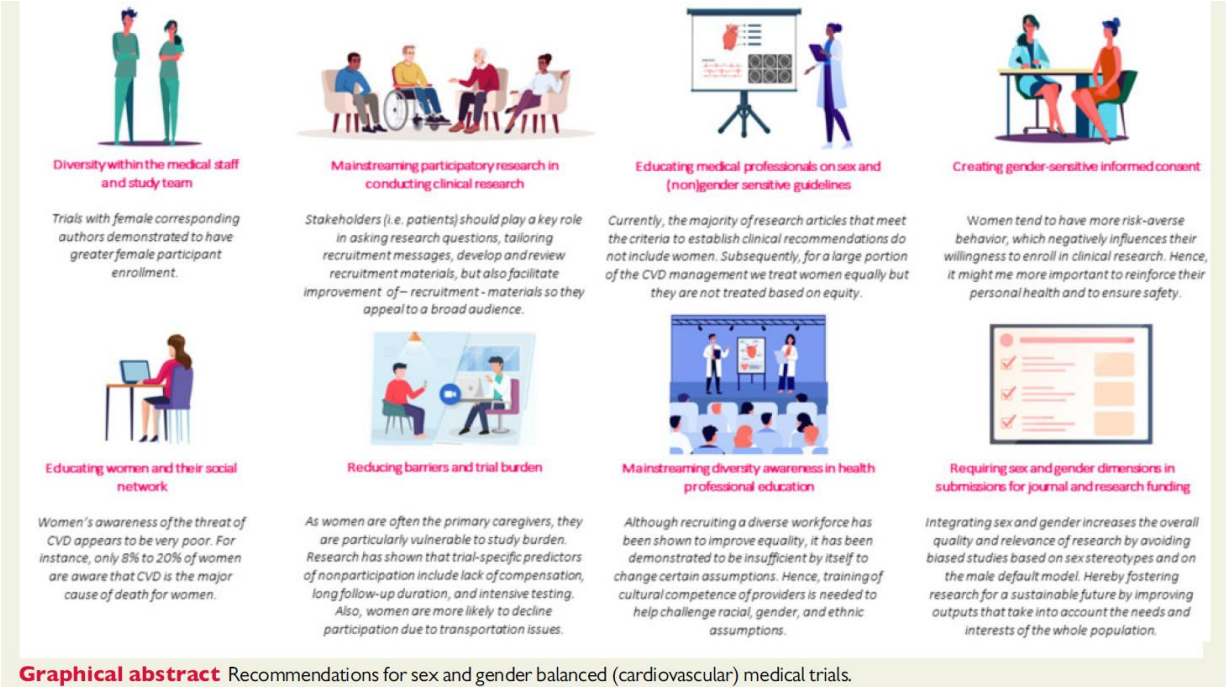
Future directions for improvement

The main hypothesis is to observe a difference in enrolment rates in LC clinical trials according to gender, in an international context.

- The study can shed light on the main barriers to enrolment in lung cancer clinical trials by providing the physician's and patient's perspective.
- By assessing the potential gender gap, we aim to identify possible areas of intervention, facilitating the allocation of resources to satisfy this unmet need of lung cancer patients.

- It will be interesting to proceed with further investigations focusing on minorities in the LGBTQIA+ community (especially transgender people, due to the anatomical and hormonal changes that influence tumor occurrence and presentation) to make healthcare as inclusive as possible.

The importance of achieving sex- and gender-based equity in clinical trials: a call to action



Graphical abstract Recommendations for sex and gender balanced (cardiovascular) medical trials.

Training of health professionals and information of patients are key points for progress!

van Diemen J, European Heart Journal 2021

ENGAGE Trial

We are ready to start… Join us!

Contacts

Principal Investigator - Silvia Novello

silvia.novello@unito.it

Referring Physicians - Maristella Bungaro, Andrea Mogavero

maristellabng@gmail.com, andrea.mogavero@unito.it

Study Coordinators - Rossana Critelli, Chiara Bellone

rossana.critelli@unito.it, chiara.bellone@unito.it